



Editorial Letter

What is gene therapy and its application in medicine?

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Abstract

The principle of Gene therapy is to correct or modify the genetic material inside a cell to treat or cure a genetic disorder or cancer. It works by adding a normal working gene, which acts by silencing an altered gene or editing a broken gene so that the body can make healthy proteins. Gene therapy is based on genetic engineering or human genetic modification. Different approaches to gene therapy are: 1. Gene transfer: Where a healthy copy of the gene. 2 replaces a faulty, disease-causing gene. Gene addition: A new or modified gene is introduced into the body to help the body fight off a disease. 3. Gene editing: Here, gene therapy inactivates or turns off a bad gene that is not working correctly. A broken or mutated gene is repaired by using specialized gene-editing tools. Tools target the main cause of conditions like inherited genetic disorders, some cancers, different neuromuscular diseases, and blood disorders instead of managing symptoms only. Somatic Gene Therapy acts by targeting modified body cells. The changes produced by gene therapy affect only the treated patient and are not passed to their children. Germ line Gene Therapy targets and changes egg, sperm, or embryo cells. These changes are heritable and passed on to their children. It is restricted or banned in many countries due to safety and ethics. CRISPR is a specific, highly precise tool used to edit genes by cutting and rewriting native DNA. CRISPR is nothing but an advanced method of gene therapy. A specific, precise tool called CRISPR edits genes by cutting and rewriting native DNA.

Main body text

Gene therapy can be called genetic engineering or human genetic modification. Gene therapies work best on genetic conditions caused by a change to a single gene. Ex. Inherited neuromuscular disorders, like Duchenne muscular dystrophy and spinal muscular atrophy. Chromosomes carry genes. Genes are the basic units carrying the physical and functional character of heredity. Nucleotides are arranged in specific sequences in a gene that encode instructions on how to manufacture proteins. If genes are altered, the encoded proteins cannot carry out their normal functions, and genetic disorders will result.

Genetic disorders are caused by a “variation” or “mutation of a gene. Not only multiple genetic changes but also environmental factors interplay in most of the genetic disorders. Defective genes responsible for disease development

can be corrected by Gene therapy. Gene therapy involves either insertion, alteration, or removal of genes within individual cells and biological tissues to treat disease. It may involve adding a normally functioning copy of the gene to affected cells, and it restores normal function. Gene therapy is a technique in medical biotechnology which modifies, replaces, or repairs defective genes within a patient’s cells which will treat or cure the underlying genetic disease instead of managing symptoms only. Gene therapy will repair a faulty gene copy by transferring a therapeutic or working gene copy into specific cells of the patient. Gene therapy provides good hope for individuals suffering from genetic disorders. Gene therapy targets the root cause of a disease and cures it. Although it was introduced in 1991, it took many decades to be introduced into medicine. Gene therapy can change the lives of people suffering from genetic disorders who have very few treatment options. The principle of human gene therapy is to modify or manipulate the

expression of a gene, which will alter the biological properties of living cells for therapeutic use.

Importance of gene therapy to targets the root cause of diseases by fixing, replacing, or turning off faulty genes rather than just managing symptoms. It is expected to provide a long-lasting cure and to halt the progress of the disease. Gene therapy is used for the treatment of genetic disorders. Genetic diseases can happen when there is a change to a gene that stops it from working normally and produces faulty proteins. Gene therapies are often one-time treatments that allow your body to make the proteins it needs to work properly and ease symptoms of a disease.

Principles of gene therapy treatment are

1. Genes responsible for the disorder must be identified first.
2. Normal gene copies are prepared.
3. These prepared gene copies are inserted into a vector
4. These vectors are made to "Infect" the affected cells.
5. Then activate these genes so that transcription and translation take place.

Gene therapy involves several mechanisms:

1. To replace a disease-causing gene with a healthy copy of the gene.
2. To introduce a new or modified gene into the body to help treat the disease.
3. To inactivate a disease-causing gene that is not functioning properly

Core Strategies:

1. **Gene Augmentation (Addition):** In gene augmentation, a healthy working copy of a gene is inserted into affected cells. It is used where a gene change prevents the cells from producing normal protein.
2. **Gene editing:** In Gene editing, special tools — like CRISPR/cas9 — are used to make precise, targeted corrections directly to existing DNA sequences, which will correct a disease-producing gene and produce correct protein.
3. **Gene silencing:** Suppresses overactive or harmful genes that prevent a normal protein from doing its job and cause cellular destruction. It suppresses the gene that is not working properly and produces disease.
4. **Gene transfer:** When an additional gene is introduced into specific cells, it is called Gene transfer. This gene is permanent as an extra piece of DNA in the cell, as it is inserted into the cell's own chromosomes to become part of the cell's own DNA.

Types of gene therapy products include:

1. **Plasmid DNA:** Circular DNA molecules are genetically modified and carry therapeutic genes into human cells.
2. **Viral vectors:** When viruses infect, they deliver genetic material into cells. Some gene therapy products are engineered from viruses. First, the viruses must be modified to remove their ability to produce infections; then these modified viruses are used as vectors (vehicles) and carry therapeutic genes into human cells.
3. **Bacterial vectors:** Bacteria can also be engineered to prevent them from producing infectious disease and then used as vectors (vehicles) to carry therapeutic genes into human tissues.
4. **Human gene editing technology:** Gene editing will disrupt harmful genes and then repair mutated genes.
5. **Patient-derived cellular gene therapy products:** Here, cells are taken from the patient and then genetically modified (a viral vector is used) and returned to the patient.

Methods of delivery and vectors

Usually, a gene cannot be directly entered into a person's cell. It must be delivered to a cell by a carrier or vector. Vectors are carrier molecules employed to enhance gene transfer efficiency in gene therapy. Currently viruses are used as most common type of vectors. They are genetically altered to carry normal human DNA. Viruses replicate by inserting their DNA into the host cell. Gene therapy uses this technology to insert genes that encode for a desired protein to create the desired trait.

- **In Vivo Delivery:** Therapeutic genetic material is injected directly into the patient's body through a targeted vector.
- **Ex Vivo Delivery:** Patient's cells are extracted and modified in a laboratory culture, and then the corrected cells are infused back into the body.

Vectors (Carriers)

- **Viral Vectors:** In modified viruses (such as Adeno-Associated Viruses or Lentiviruses), the disease-causing traits are removed and modified to efficiently transport genes into host cells. Viral vectors use harmless and modified viruses (like retroviruses or adenoviruses) because they can enter cells easily.
- **Non-Viral Vectors:** Here, synthetic alternatives are employed to reduce immune system reactions and improve safety. Non-viral vectors use chemical or physical methods like lipid nanoparticles or polymers to insert DNA into cells.

The important steps of gene therapy include laboratory preparation and patient treatment: The first step is inserting a functional gene copy into a vector; next is to collect the patient's

stem cells (apheresis); then add the vector to the stem cells in a laboratory, followed by conditioning the patient's body with chemotherapy, and lastly, to infuse the modified cells back into the patient.

Initial laboratory preparation followed by treatment:

Step 1: Vector Insertion — in the laboratory, copies of healthy, functional genes are placed inside a vector, the delivery vehicle, which is a modified viral vector.

Step 2: Cell Collection — by a procedure called apheresis or bone marrow extraction, the stem cells or blood cells are harvested from the patient.

Step 3: Genetic Modification — then the vector containing the healthy gene is mixed with the patient's collected stem cells in the laboratory so that the stem cells can absorb the new genetic material.

Step 4: Patient Conditioning — the patient is primed with a short course of chemotherapy or suitable medications to suppress the immune system.

Step 5: Infusion/Reintroduction — the newly modified, healthy cells are then infused back into the patient's bloodstream and allowed to multiply, and they will correct the genetic defect.

The viruses vectors used for genetic modifications are

1. Adenovirus
2. Adeno-associated virus
3. Retrovirus
4. Lentivirus.

Adenovirus advantages are

1. They can rapidly infect large numbers of human cells
2. It has got low pathogenicity in humans
3. It can hold large segments of DNA
4. Its Genomes do not undergo any rearrangement at high rates
5. Their DNA is easy to manipulate with present recombinant techniques

Stem cell therapy: Stem cells are unspecialized foundation cells in the body that can divide endlessly. They can transform into any type of cells in the body. They can renew and multiply and transform into other types of cells like muscle, brain, heart, etc. It is divided into embryonic stem cells and Somatic stem cells.

1. **Embryonic stem cell therapy** [Germline gene therapy]: Here the reproductive cells (sperm, eggs, or early embryos) are modified, and the genetic changes are heritable and passed on to their children. It involves

permanent transfer of the gene to the sperm or egg cells. Its use is restricted and banned in most countries due to safety and ethics.

Embryonic stem cell derived from 4 to 5 days old embryo which is in the blastocyst phase of development. They are obtained from embryos of in vitro fertilisation clinics where many eggs are fertilised and implanted into women.

2. **Somatic stem cells:** Somatic stem cells exist after embryonic development. They are found in many tissues like brain, bone marrow, blood, liver, etc. In Somatic cell gene therapy, the DNA of non-reproductive body cells (like lung or blood cells) is altered to treat the patient, and changes are not passed to future generations. It involves the transfer of healthy genes to the affected cells. It is conservative and safe, as it affects the targeted cells only. It is not transmitted to future generations. Sometimes the patient's own blood stem cells are taken and altered them and introduced back into his body.

Where gene therapy can be used:

- **Monogenic Disorders:** It can treat single-gene inherited conditions like haemophilia, combined immunodeficiencies, and muscular dystrophy.
- **Oncology:** Advanced immunotherapies where T-cells are modified, which can identify and destroy cancer cells.
- **Acquired and Degenerative Conditions:** Further research is done to treat inherited retinal blindness and many cardiovascular or neurological disorders.

Delivery or Application Methods:

They are categorised based on the type of cells targeted or the method of their delivery into the body.

- a) Somatic cell gene therapy,
- b) Germline gene therapy,
- c) *in vivo* gene therapy, and
- d) *in vitro* gene therapy.

In vivo gene therapy: Delivers the new therapeutic genetic material directly to the target cells in the patient's body via a vector (ex., an engineered virus) injected into the target tissue or bloodstream. The difficulty is in ensuring specificity and reaching the correct target cells [cells containing defective genes] within the body.

In vitro gene therapy: Target cells are extracted from the patient, modified with the genetic correction in a laboratory setting, multiplied, and infused back into the patient. After selection and amplification, the cells are returned to the body. This method is safe; it depends upon the type of cells being targeted.

A newer approach called Genome editing allows precise correction or other targeted changes to the DNA in cells to restore a cell's normal function. CRISPR is a specific, highly precise tool that edits genes by cutting and rewriting native DNA. CRISPR is a recent advanced method of gene therapy.

Gene therapy in clinical use:

1. Gene therapies will work best when the changes are produced by a single gene. Ex. Single-Gene (Monogenic) Disorders are Cystic fibrosis, Sickle cell disease, Huntington's disease, Haemophilia.
2. Young children suffering from spinal muscular atrophy are treated by giving Zolgensma (Onasemnogene APOBAPARVOVEC), which delivers a healthy gene and fixes the faulty gene.
3. Skysona (Elivaldogene AUTOTEMCEL), using modified stem cells, slows early cerebral adrenoleukodystrophy.
4. Luxturna (Voretigene NEPARVOVEC): treats progressive blindness caused by inherited retinal disease.
5. Blood and Immune Disorders are treated by Zynteglo (Betibeglogene AUTOTEMCEL), which treats beta-thalassemia by adding a working beta-globin gene to bone marrow cells.
6. Haemophilia B is treated with Hemgenix (Etracogene DEZPARVOVEC), which provides a functional gene to the liver so it can produce blood-clotting factors.
7. Sickle Cell is treated by Gene Therapies which edit or add genes in blood stem cells to stop red blood cells from misshaping.
8. Yescarta (Axicabtagene CILOLEUCEL) reprograms a patient's own immune T-cells outside the body to hunt and destroy lymphoma cells.
9. Leukaemia and lymphoma are treated by giving Kymriah (Tisagenlecleucel), which uses modified T-cells.
10. Advanced bladder cancers are managed by giving Adstiladrin (Nadofaragene FIRADENOVEC) which delivers a specific gene via a viral vector.
11. Down syndrome (an extra chromosome 21. It leads to learning delays and unique facial traits. Tay-Sachs disease (destruction of the nervous system), and Turner syndrome (where an X chromosome is absent in females. It produces short stature and heart disease).
12. Severe Combined Immunodeficiency (SCID): Reconstructs missing immune cell functions in infants.
13. Metachromatic Leukodystrophy (MLD) & Cerebral Adrenoleukodystrophy (CALD): Halts deadly brain degeneration in young children.

In Traditional Gene Therapy, it adds a healthy, working copy of a gene into a cell using a carrier (usually an engineered

virus). It does not alter the original, faulty DNA sequence. It simply provides a backup copy so the cell can make the correct protein. It fades over time in dividing cells because the added gene does not always integrate into the host genome. Examples: Luxturna for inherited blindness and Zolgensma for spinal muscular atrophy

CRISPR Gene Editing uses a guide RNA and a protein (like Cas9) to find an exact spot on the DNA and act as molecular scissors. It directly cuts, removes, corrects, or inactivates specific faulty DNA sequences rather than just adding a supplement. The changes are permanent because the native genome itself is rewritten. Examples: For sickle cell disease, Casgevy is used, which uses CRISPR to turn off a faulty gene. In inherited genetic disorders (monogenic diseases), gene therapy replaces the single broken or missing gene with a healthy copy. Immunotherapy modifies the patient's own immune cells (like CAR-T cell therapy) to target and destroy cancer cells. Oncolytic Gene Therapy uses specially modified viruses to target, enter, and kill tumour cells directly and spares healthy tissue.

Advantages of Gene therapy:

1. To give a normal life to a baby born with a genetic disorder.
2. Good effects are passed down through generations when we remove a faulty gene from a parent; they won't transfer this gene to their kids.
3. Research is on the way to give healthy life to cancer patients by gene therapy. ex. BRCA women.
4. Some hereditary diseases may not have a cure except for gene therapy.
5. Gene therapy can provide new treatments for diseases that currently don't have many other options.
6. It is convenience as most gene therapies are one-time treatments does not require prolonged repeated treatment.
7. If gene therapy is started earlier in the course of an illness can prevent the disease and the serious damage.
8. Gene therapy focuses on the root cause treat the cause and not just the symptoms alone. Ex. Vitiligo

Emerging Research Areas and Research direction:

Current research in gene therapy focuses on precision editing, improving targeted delivery systems, and to treat cancer, heart diseases, and infectious diseases

1. Advances in Genome and RNA Editing Tools

- a) Base and Prime Editing: After the present standard DNA double-strand break methods (like CRISPR-Cas9) research is done on base editing and prime editing, which allows single-nucleotide conversions or insertions which do not cut the DNA backbone, reduces risks of off-target.

- b) Editing of RNA and Epigenome: By using RNA-targeting enzymes (ex. ADAR or Cas13) and epigenetic modulators (CRISPRa/i) to alter protein expression temporarily or silence genes without producing permanent genomic changes.
- c) Editing of Mitochondrial Genome: By developing and using targeted nucleases and double-stranded DNA deaminase base editors (DdCBE/TALED), maternally inherited mitochondrial DNA disorders can be managed.

2. Next-Generation Delivery Systems

Targeted Viral Vectors: Further research is being done by genetically engineering a safer and tissue-specific Adeno-Associated Virus (AAV) to cross physiological barriers (such as the blood-brain barrier) and prevent immunotoxicity.

Production of Non-Viral and Nanoparticle Platforms: By advancing virus-like particles (VLPs), ionizable lipid nanoparticles (LNPs) and polymer-based delivery vehicles will improve cargo capacity and reduce manufacturing costs and allows multiple dosing.

AI-Driven Vector Design: Artificial intelligence to help to know the off-target effects and optimize RNA motif structures, and design customized capsid shells for specific human organs.

3. Broadening Clinical Applications

- a) In Oncology & Immunotherapy, gene therapy is broadened by developing CAR-T cell therapy and engineered natural killer (NK) cells, together with tumor-suppressor gene restoration (e.g., p53) and advance suicide gene strategies to identify and destroy cancer cells.
- b) In Infectious Disease Control, gene therapy can be modified to utilize CRISPR-based strategies and RNA interference (RNAi) to achieve functional remission or resistance against HIV, Hepatitis B (HBV), and multidrug-resistant (MDR) bacterial biofilms.
- c) In Common Chronic Disorders, research can be expanded from managing rare monogenic conditions (ex. sickle cell disease) by gene therapy into treating high-prevalence polygenic conditions (ex., neurodegenerative diseases (Huntington's) and diabetes)

4. Research to overcome Clinical hurdles and manufacturing costs.

- a) Cost Reduction: Research to be done to improve ex vivo and in vivo manufacturing pipelines for cost reduction.
- b) Immune Evasion: Further research is required in gene therapy for producing therapeutic proteins, viral capsids, and editing machinery that can bypass host immune recognition. Re-administration of Gene therapy gives a high therapeutic response by targeting and correcting the root molecular causes of single-gene and hematologic disorders than managing symptoms only.

Safety concerns;

- a) High cost. Gene therapy is costly and not affordable for many people.
- b) Experimental. Gene therapy is still in an evolving stage, and we do not know about its efficacy, safety, side effects, and long-term effects on future generations. There are no guarantees of a cure.
- c) It can be potentially dangerous. There is some concern that gene therapy can affect other normal cells in the body causing harmful side effects. It may affect reproductive cells without detection, and these changes are passed on to people's children.
- d) Ethical issues arise because of the above constraints.
- e) May produce infection. When we use inactivated viruses, to carry healthy genetic material into a faulty cell in the body can infect the person.
- f) Availability: Gene therapies are not available in developing nations due to cost and access to technology.

Ethical consideration: When treating patients with gene therapy, we must consider many ethical issues.

The Gene therapy must balance medical advancement against safety, informed consent, and its impact on the general population.

- a) Somatic Gene Therapy targets non-reproductive body cells. It is less controversial changes as it affects only the individual patient and are not passed down to children.
- b) Germline Gene Therapy will alter eggs, sperm, or early embryos, and the changes are permanent and heritable. Changes are passed to all future generations. It involves safety and moral objections, as the unborn children cannot provide informed consent. The long-term developmental side effects or mutations are unpredictable. We must consider the risks to safety and unwanted consequences.
- c) Sometimes, tools like CRISPR/Cas9 or viral vectors can inadvertently cut or alter unintended parts of the genome, risking insertional mutagenesis or cancer.
- d) Another risk is the durability of genetic changes.
- e) Delayed adverse effects.

Informed consent

- a) As the gene therapy is in evolving stage to explain the permanent nature of gene manipulation and unpredictable changes in the gene make it difficult to get voluntary informed consent.
- b) As patients or parents of critically ill children want some form of treatment out of desperation, they will give consent without evaluating risks versus benefits.

- c) Because of high cost affects the Distributive Justice and Access Equity Health. Gene therapy is available to wealthy individuals in developed nations and not in lower-income regions.
- d) We must differentiate between enhancement and treatment distinguishing Boundaries.
- e) Using gene therapy to cure monogenic or debilitating diseases is accepted, but using it for boosting height, intelligence, or athletic prowess should not be used and must be restricted or condemned.
- f) Neo-Eugenics: Pushes the risk of societal pressure to fit a genetic "ideal," potentially discriminating against individuals with disabilities or natural differences. Neo-Eugenics shapes human populations using modern reproductive and genetic technologies instead of sterilization or selective breeding. It will lead to the unethical production of ideal or super humans, which discriminates against normal individuals in favor of genetically modified human beings.
- g) If data Privacy is not maintained it will lead to Genetic Discrimination. The Insurers, employers may get access to individual's genetic profile about individuals' genetic vulnerabilities and use it to exploit in denying insurance coverage, jobs opportunities.

Ethical consideration and informed consent

Today, through genetic counselling, genetic diseases are prevented not cured. (e.g., If both parents have heterozygous trait for a serious recessive disorder, choose not to conceive. If homozygous for the disorder chooses to terminate the pregnancy of a foetus.

Autonomy

To do genetic testing adequate information must be provided about the risks, benefits, and efficacy. If carrier status testing is being proposed to be done for pregnant woman or prenatal testing for her foetus, she must be informed whether the disorder can be prevented or treated so that she can a decision whether to abort. Sometimes mandatory newborn screening is very useful to ensure that all children get the benefits of screening for PKU and hypothyroidism, where early treatment can make the child well by preventing mental retardation.

The important ethical consideration is to cure a genetically inherited disease and not to select sex or characteristics of a baby, height, weight, IQ, etc. Embryo selection can be done for disorders like Huntington's disease. Cystic fibrosis or sickle cell anaemia. There is a dilemma about how to dispose of the unused embryos.

Disclosing genetic information to spouses

In most situations, the tested individual will share that information with the other spouse. When a married individual

is diagnosed as having the allele for a serious recessive disorder, the spouse might claim that the health care provider has a duty to share that information with him or her to facilitate reproductive decision-making.

Disclosing genetic information to relatives

The strongest case for a warning would exist when there is a high likelihood that the Blood relatives have the genetic defect, the defect presents a serious risk to the relative, and there is reason to believe that the disclosure is necessary to prevent serious harm. Ex. Malignant hyperthermia is an autosomal dominant genetic condition causing a fatal reaction to common anaesthesia. Prompt warning of families can literally save lives.

Ethical issues with gene therapy:

- a) It is difficult to predict the good and bad effects of gene therapy.
- b) Who must decide which is normal and what is not?
- c) High cost of therapy. Producing efficient gene therapy requires a lot of money.
- d) Can gene therapy be used to enhance basic human traits like height, weight, intelligence, or athletic ability?
- e) Because of the above reasons, governments do not encourage germline gene therapy. Germline treatment is not permitted by all countries.
- f) Clinical gene therapy is not available in low- and middle-income regions where incidence of genetic disorders is high.
- g) Immune Safety: There is some concern about refining capsids and dosages to eliminate either acute or delayed adverse immune responses.

Conclusion

Gene therapy is a medical technique that treats or prevents disease by fixing, replacing, or turning off faulty genes inside a person's cells. If the body's DNA is considered an instruction book, gene therapy corrects a typo or adds a missing page so the cells can work correctly. Gene therapy can cure a disease by replacing, fixing, or adding genes inside a patient's cells. Gene therapy treatment is used for Cerebral adrenoleukodystrophy. Inherited blood disorders: sickle cell anaemia, thalassemia and haemophilia, Inherited Neuromuscular diseases like spinal muscular atrophy and Duchenne muscular dystrophy, Inherited retinal (eye) diseases, like Leber's congenital amaurosis, Metachromatic leukodystrophy. Much research is being done to treat many genetic conditions, as well as HIV and cancer, by gene therapy. Hurdles faced are very high Costs, Global Access, and Immune Safety.